REMARKS

This Reply is in response to the Final Office Action dated July 21, 2003. This Reply is timely filed.

Claims 1-19 were pending at the time of the Office Action. In the Office Action, claims 1-11 were all rejected and claims 12-19 deemed constructively restricted and thus withdrawn from consideration by the Examiner. In this Reply, no claims have been amended or added, while claims 13-19 have been cancelled, without prejudice. No new matter has been added.

Now turning to rejections based on art, claims 1-11 were rejected under 35 U.S.C. 103(a) as being unpatentable Kataoka (Anal. Chem., 71:4237-4244 (October 1, 1999)) in view of Chong (Anal. Chem., 69:3889-3898 (1997)) and either Wang (Anal. Chem., 69:4566-4576 (1997)), or Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, pg. 54 (1997).

The Examiner concludes:

> It would have been obvious to use sol gel in Kataoka (Anal. Chem., 71:4237-4244 (October 1, 1999)) because Chong (Anal. Chem., 69:3889-3898 (1997) discloses sol gel chemistry allow low costs, has the unique ability to achieve molecular uniformity, and has a strong adhesion of the coating to the substrate and either because Wang (Anal. Chem., 69:4566-4576 (1997)) (Abstract) discloses that sol gel coated columns provide efficient *separation* for analytes from a wide polarity range and because of direct chemical bonding to fused silica substrates sol-gel coatings possess significantly higher thermal stability than conventional coatings or because Malik (Advanced Sol-gel Column Technology for Condensed-phase *Microseparations*, (1997 page 54) discloses the advance features of sol-gel chemistry can effectively be applied in an open column and chemical bonding of the coating or the monolithic bed to the column walls provides enhanced operational stability to the sol-gel columns. (italics for emphasis)

It is first noted that inventor Dr. Malik is a co-author of all references cited above (Chong, Wang and Malik), except Kataoka. Before reviewing the cited art, Applicant will first briefly review the claimed invention as recited in claim 1. Claim 1 recites a method of preconcentrating trace analytes and includes the steps of providing a hollow capillary having at least one sol-gel extraction medium within the hollow capillary. Preconcentrating is an extraction process which is distinct from separation processes. Moreover, devices for separation and devices for extraction are distinct and non-interchangeable, as explained below.

To provide reasonable capacity suitable for extraction, those having ordinary skill in the art know that extraction devices need coatings on the order of microns, and preferably tens of

microns. However, coatings on the order of microns or tens of microns generally reduce separation efficiency. This is why the stationary phase coating thickness disclosed in the separation devices cited by the Examiner are on the order of 0.25 μm.

In a typical microextraction process, trace analyte is isolated and preconcentrated from complex multi-component matrices by generally awaiting equilibrium to be reached. In contrast, in a separation process, multi-component mixtures having different interaction strengths with the stationary phase coating is required for separation.

In the claimed method, the sol-gel extraction medium is *chemically bound* to inner walls of the hollow capillary to form a sol-gel extraction medium-loaded capillary. An important step disclosed by Applicant in the formation of the sol-gel coated capillary is a hydrothermal treatment step of the capillary inner surface prior to coating. (See, for example, page 22, line 20 to page 23, line 20).

Hydrothermal treatment of the capillary inner-surface begins with treatment of the inner-surface thereof with deionized water. This initial hydrothermal treatment is performed for several reasons. First, the water serves to clean the inner capillary surface, removing any contaminants originating from the capillary drawing process (e.g. 2000° C) or postdrawing manipulation and handling. Moreover, this pretreatment with water enhances surface silanol concentrations, thereby offering a higher percentage of bonding sites for anchoring the sol-gel coating to the inner capillary surface.

Without the hydrothermal treatment step, insufficient bonding sites are available to provide chemically immobilized (stable) sol-gel coatings on the capillary inner surface. As a result, coatings without the hydrothermal treatment step are prone to dislodging from the capillary surface. The tendency for the coating to dislodge increases as the coating thickness increases. None of the cited references disclose a hydrothermal treatment step.

Relatively thick sol-gel coatings made possible by the hydrothermal treatment step are taught by Applicant as they lead to enhanced extraction sensitivity. For example, page 34, lines 15 to 25 are copied below:

Sol-gel coating technology can easily produce thick coatings (Chong, S.L.; Wang, D.-.X.; Hayes, J.D.; Wilhite, B.W.; Malik, A. *Anal. Chem.* **1997**, *69*, 3889-3898; Wang, Z.Y.; Xiao, C.H.; Wu, C.Y.; Wu, C.; Han, H. *J. Chromatogr. A* **2000**, *893*, 157-168; Zeng, Z.; Qiu, W.; Huang, Z. *Anal. Chem.* **2001**, *73*, 2429-2436) (d_f>1 μm). For example, Zeng *et al.* recently reported SPME on sol-gel coated fibers with a coating thickness of 76 μm. The use of microextraction capillaries with thick sol-gel coatings should lead to higher sensitivity of capillary microextraction as will

be demonstrated in an upcoming paper. (Medlar, J.; Kabir, A.; Malik, A. *Work in Progress*) It can be expected that the use of capillaries with larger inner diameter and thicker sol-gel coatings should lead to further enhancement of this extraction sensitivity.

The sol-gel loaded capillary is exposed to a sample containing at least one target analyte, wherein the target analyte becomes disposed inside the hollow capillary. The invention provides unexpectedly high detection sensitivities. For example, According to page 42, line 22 to 24, the invention provides parts per trillion (ppt) and parts per quadrillion (ppq) level detection sensitivities for both polar and non-polar analytes. Amended claim 4 recites the sol-gel extraction medium comprises a porous sol gel monolithic bed.

According to the Examiner regarding Kataoka:

At best, the claims differ from Kataoka (Anal. Chem., 71:4237-4244 (October 1, 1999)) in reciting use of sol gel.

Later (page 6) in the Office Action, the Examiner asserts that:

The [Applicant's] remarks [in the reply filed on June 9, 2003] urge that Kataoka (Anal. Chem., 71:4237-4244, 1999) is directed to physically bonded capillaries. However, this appears to be a mere allegation unsupported by fact. Kataoka would appear to be silent on the issue of chemical bonding.

Applicant notes that the Examiner is correct that Kataoka does not disclose use of sol-gel coatings. However, Applicant respectfully disagrees with the Examiner's assertion above regarding the type of bonding present between Kataoka's coatings and the capillaries.

Kataoka does disclose coated capillaries for performing in-tube solid-phase microextraction, as does the claimed invention. However, the microextraction device and methods disclosed by Kataoka differ significantly from the claimed invention. Kataoka discloses use of 60 cm segments of commercial gas chromatography (GC) capillary columns as extraction tubes. Two types of GC capillaries were used: Omegawax 250 and SPB 5. In such capillaries, the extraction medium was a thin (page 4241 col. 1; 0.25 μm in thickness) coating. The coating was thin because the coated capillaries were intended for use as separation devices which generally require thin coatings.

Regarding the Examiner's assertion that Kataoka *inherently* discloses chemically bonded capillaries, Applicant respectfully disagrees that Kataoka provides the proper foundation for such an assertion. Now turning to the MPEP regarding inherency, MPEP 2112 is entitled "Requirements of Rejection Based on Inherency; Burden". According to this Section in relevant part:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)(reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). (large font for emphasis only) "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the preform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was biaxially oriented. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented synthetic plastic material." Id. at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. *The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.* (italics for emphasis)

In view of the above case law and MPEP, since the Examiner did not provide any objective evidence or cogent technical reasoning to support the conclusion of inherency, the assertion of chemical bonding based on inherency is improper.

In addition, inherency (when properly supported) is only proper for a 102 rejection, not for a 103 rejection, as is asserted herein. There is no such thing as "inherent obviousness," since inherence and obviousness are different legal concepts. See In re Spormann, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information

"is not necessarily known . . . . [and] Obviousness cannot be predicated on what is unknown." Id. Thus, the inherency based obviousness rejection of claim 1 is improper.

Although not required to rebut the inherency assertion, Applicant will present objective evidence and cogent technical reasoning below to prove that Kataoka only discloses physical bonded capillaries (as opposed to chemically bonded capillaries). For the Omegawax 250 capillary the stationary phase coating is known to be polyethylene glycol, while the stationary phase for the SPB 5 capillary is known to be polysiloxane. These coatings free radical crosslink and become physically immobilized on the capillary inner surface, not chemically bonded to the GC tube surface as there are no reactive groups to chemically bond either of these coatings to the capillary wall material. Thus, the coatings used by Katoaka being commercially prepared stationary phase coatings in GC columns, are physically held, not chemically bonded to the capillary inner surface. Because of the absence of direct chemical bonding between the stationary phase coating and the GC capillary inner walls, the thermal and solvent stabilities of such coatings are typically poor or at best moderate.

According to the Examiner regarding Chong:

Chong (Anal. Chem., 69:3889-3898 (1997) discloses sol gel chemistry allows low costs, has the unique ability to achieve molecular uniformity, and has a strong adhesion of the coating to the substrate.

Applicant agrees that Chong discloses sol-gel chemistry. However, the fiber-based microextraction format described in Chong is quite different and teaches away from the hollow capillary microextraction method claimed in the present application. In the fiber-based format of Chong, the sol-gel coating is applied by dipping the fused silica fiber rod. As a result, the outer surface of the fused silica rod (solid rod with no hole) becomes coated with sol-gel. In contrast, in the claimed capillary microextraction format of the claimed invention, the sol-gel extraction medium is chemically bound within a hollow capillary either in the form of a sol-gel surface

coating (claim 1) or a porous sol-gel monolithic bed (claim 4). In addition, Chong does not disclose a hydrothermal treatment step.

Moreover, Katoaka and Chong are not readily combinable. Katoaka is based on a hollow GC tube, while Chong discloses a solid rod. Chong dip coats the outside of a solid rod to coat the rod, while Kataoka coats the inside of a hollow GC tube. Chong's dip coating method cannot be used to coat the inside of a hollow tube narrow diameter tube.. Thus, Katoaka and Chong are not combinable, nor is Chong combinable with any other cited reference, which are all hollow tube references.

Turning now to Wang, according to the Examiner regarding Wang:

> Wang (Anal. Chem., 69:4566-4576 (1997)) (Abstract) discloses that sol gel coated columns provide efficient *separation* for analytes from a wide polarity range and because of direct chemical bonding to fused silica substrates sol-gel coatings possess significantly higher thermal stability than conventional coatings. (italics for emphasis)

Applicant agrees that Wang discloses chemically bonded sol-gel coated gas chromatography (GC) columns for *separation*. However, as noted above, separation and the claimed microextraction process are quite different processes, as are the devices for practicing the respective methods. Wang's disclosed GC separation columns have a sub-micrometer sol-gel stationary phase film thickness of about 0.25 μm. Although efficient for separation as noted correctly by the Examiner, those having ordinary skill in the art would realize that the thin coating makes the capacity and resulting sensitivity of Wang's GC device unsuitable for extraction. Moreover, although thickening the stationary phase layer would tend to improve extraction capacity, substantially thicker layers (e.g. on the order of at least microns) would lead to serious adherence problems. Thus, it is not surprising that Wang discloses use of the coated GC column for only separation, and not for microextraction.

Moreover, Wang does not disclose a hydrothermal treatment step. Without a hydrothermal treatment step, the coating will be weakly bound to the GC tube, even for the disclosed thin coating of only 0.25 μm. As noted earlier, the tendency for the coating to dislodge increases as the coating thickness increases. Thus, Wang's separation device and method teach

away from use of the disclosed separation device as an extraction device for extracting a trace analyte, and is thus not reasonably combinable with either Kataoka or Chong.

Turning now to Malik, According to the Examiner:

Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, (1997 page 54) discloses the advance features of sol-gel chemistry can effectively be applied in an open column and chemical bonding of the coating or the monolithic bed to the column walls provides enhanced operational stability to the sol-gel columns.

Malik discloses the use of very small diameter sol-gel columns (25-μm and 50-μm internal diameter) for capillary electrophoretic *separations,* not for in-tube SPME or for sample preconcentration in general. The coating thickness used was less than 1 micron. In contrast, Applicant discloses a 250-μm internal diameter capillary in FIGs. 11 and 15 and accompany disclosure. Microseparation techniques are far different from microextraction techniques as are the devices disclosed by Malik for capillary electrophoretic separations. It is well known in the art that capillary electrophoresis techniques require that the separation column be of a sufficiently small internal diameter to avoid excessive Joule heating. For extraction, however, such small diameter capillaries are not suitable since the sample capacity of such small diameter capillaries will be exceedingly low which results in severely diminished sample capacity and extraction sensitivity.

No mention is made in Malik as to whether the disclosed coated capillary electrophoresis columns can also be used for microextraction. However, as evidenced by the Malik paper's only reference to microextraction being to the coated solid rod disclosed by Chong (cited herein) in the last sentence of paragraph 1, the Malik paper strongly teaches that the coated capillary columns disclosed therein are not suitable for microextraction. Thus, Malik teaches away from Applicant's claimed extraction method using a sol-gel extraction medium-loaded capillary having sol-gel extraction medium chemically bound to inner walls of the capillary.

Moreover, like Chong and Wang, Malik does not disclose the hydrothermal treatment important for the creation of stable coating or monolithic bed inside the fused silica capillary. Thus, Malik's separation device and method teach away from use of the disclosed separation device as an extraction device for extracting a trace analyte, and is thus not reasonably combinable with either Kataoka or Chong.

In view of the above, amended claim 1 and its respective dependent claims are believed to be patentable claims.

Claim 4 recites the sol-gel extraction medium comprises a porous sol gel monolithic bed is believed to provide an independent basis for patentability. Claim 4 was rejected under 35 U.S.C. 103(a) as being unpatentable over Kataoka (Anal. Chem., 71:4237-4244 (October 1, 1999)) in view of Chong (Anal. Chem., 69:3889-3898 (1997) and either Wang (Anal. Chem., 69:4566-4576 (1997)), or Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, pg. 54 (1997) as applied to claims 1-11 above, and further in view of Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, (1997 page 54) or Nakanishi (U.S. Patent No. 5,624,875).

According to the Examiner:

At best, the claim differs from Kataoka (Anal. Chem., 71:4237-4244 (October 1, 1999)) in view of Chong (Anal. Chem., 69:3889-3898 (1997) and either Wang (Anal. Chem., 69:4566-4576 (1997)), or Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, pg. 54 (1997) in reciting use of a monolith. Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, pg. 54 (1997) discloses open tubular columns and monolithic columns are interchangeable alternatives to apply the advanced features of sol gel chemistry. Nakanishi (U.S. Patent No. 5,624,875) (column 4, lines 25-27 and column 6, lines 39-46) discloses that sol gel columns have very low flow resistance.

The Examiner thus concludes that:

It would have been obvious to use a monolith in Kataoka (Anal. Chem., 71:4237-4244 (October 1, 1999)) in view of Chong (Anal. Chem., 69:3889-3898 (1997) and either Wang (Anal. Chem., 69:4566-4576 (1997)), or Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, pg. 54 (1997) either because Malik (Advanced Sol-gel Column Technology for Condensed-phase Microseparations, (1997 page 54) discloses open tubular columns and monolithic columns are interchangeable alternatives to apply the advanced features of sol gel chemistry or because Nakanishi (U.S. Patent No. 5,624,875) (column 4, lines 25-27 and column 6, lines 39-46) discloses that sol gel columns have very low flow resistance.

Nakanishi does disclose a porous sol-gel monolithic bed. However, Nakanishi the disclosed sol-gel monolithic columns are not chemically bound to the tubes and are used for liquid chromatography separation, not for extraction. The monolithic bed disclosed in Nakanishi is not in the capillary format. It is also unlikely the sol-gel technology described in Nakanishi can be applied to a capillary format since the diameter of the separation beds described therein are 4.6 mm and 6.0 mm respectively compared with the typical diameter of the bed in the capillary format is on the order of 0.25 mm.

The method disclosed in Nakanishi for the preparation of monolithic column is also very different from the method used in the present invention and renders the resulting device incapable of having a chemically bound monolithic column. The method developed in Nakanishi discloses a number of steps: (a) preparing sol-gel silica material using a sol solution, (b) treating the prepared sol-gel silica material with ammonia solution (for seven days), (c) heating the created sol-gel material to high temperature (600 – 800° C), (d) Using the created silica material to prepare cylindrical rods either by placing the sol solution in a cylindrical mold (6 mm) or by mechanically shaping the solid sol-gel silica (4.6 mm diameter), and (e) securing the silica rod inside a tube, (e) Derivatizing the silica rods using conventional silane chemistry to chemically bind a chromatographically favorable organic ligand to the surface of the created silica rod.

The porous monolithic bed in Nakanishi cannot be secured via chemical bonding since the stainless steel or plastic tube lacks functional groups needed for chemical bonding with monolithic bed. In contrast in the claimed invention, a hollow tube (e.g. fused silica) is used to prepare the monolithic column. As disclosed in the present Application, silanol groups on the inner surface of such a tube can serve as the chemical binding sites for the porous monolithic bed in the course of its in situ creation from a sol solution. Such chemical bonding provides added operational stability and prolongs the lifetime of the sol-gel monolithic capillary.

Also, the method described in Nakanishi is not adapted for the preparation of sol-gel monolithic silica beds within a fused silica capillary because Nakanishi uses high temperature heating (600-800 C). Under such high temperature conditions the protective outer coating of the fused silica capillary will be damaged rendering it very fragile for practical operation. Accordingly, Nakanishi's monolithic bed is not combinable with any of the other cited references. Therefore, claim 4 provides a limitation that is believed to be independently patentable.

Applicant has made every effort to present claims which distinguish over the cited art, and it is believed that all pending claims are in condition for allowance. However, Applicant requests that the Examiner contact the undersigned after review of this Reply if the Examiner

determines that any clarification is necessary to permit issuance of a Notice of Allowance.

Respectfully submitted,

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